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Melanoma risk and survival among organ transplant recipients

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Abstract

Solid organ transplant recipients, who are medically immunosuppressed to prevent graft rejection, have increased melanoma risk, but risk factors and outcomes are incompletely documented. We evaluated melanoma incidence among 139,991 non-Hispanic white transplants using linked U.S. transplant-cancer registry data (1987–2010). We used standardized incidence ratios (SIRs) to compare incidence to the general population, and incidence rate ratios (IRRs) from multivariable

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Conflict of Interest

All authors declare no conflict of interest.

Poisson models to assess risk factors. Separately, we compared post-melanoma survival among transplant recipients (N=182) and non-recipients (N=131,358) using multivariable Cox models. Among transplant recipients, risk of invasive melanoma (N=519) was elevated (SIR=2.20, 95%CI 2.01-2.39), especially for regional stage tumors (SIR=4.11, 95%CI 3.27–5.09). Risk of localized tumors was stable over time after transplantation, but higher with azathioprine maintenance therapy (IRR=1.35, 95%CI 1.03–1.77). Risk of regional/distant stage tumors peaked within 4 years following transplantation and increased with polyclonal antibody induction therapy (IRR=1.65, 95%CI 1.02–2.67). Melanoma-specific mortality was higher among transplant recipients than non-recipients (HR 2.98, 95%CI 2.26–3.93). Melanoma exhibits increased incidence and aggressive behavior under transplant-related immunosuppression. Some localized melanomas may result from azathioprine, which acts synergistically with ultraviolet radiation, while T-cell depleting induction therapies may promote late stage tumors. Our findings support sun safety practices and skin screening for transplant recipients.

Introduction

Melanoma is an aggressive form of skin cancer whose rapidly increasing incidence represents a major public health concern in the United States (Siegel *et al.*, 2014; United States Department of Health and Human Services, 2014). Risk factors include older age, family history, fair complexion, exposure to ultraviolet radiation (UVR) (Rhodes *et al.*, 1987), and higher counts of nevi (Olsen *et al.*, 2010). Accordingly, incidence is concentrated in non-Hispanic white persons (Cormier *et al.*, 2006), and among this group increases with decreasing latitude of residence (Eide and Weinstock, 2005).

Melanoma risk has been reported to be increased two- to five-fold among solid organ transplant recipients, who are prescribed immunosuppressive medications to prevent graft rejection (Grulich *et al.*, 2007; Dahlke *et al.*, 2014; Engels *et al.*, 2011; Jensen *et al.*, 1999; Chatrath *et al.*, 2013; Kasiske *et al.*, 2004; Hollenbeak *et al.*, 2005). This elevation could result from immune dysfunction or from direct carcinogenic effects of some medications (O'Donovan *et al.*, 2005; Hojo *et al.*, 1999; Han *et al.*, 2012). In addition, transplant recipients are screened intensively for skin cancer due to a very high risk of cutaneous squamous cell carcinoma (SCC) (Ulrich *et al.*, 2008). Thus, the melanoma excess could partly represent overdiagnosis, in which case it should be most pronounced for early stage tumors (Welch *et al.*, 2005).

Furthermore, immune response may be important in controlling melanoma after diagnosis. This possibility is supported by the recent success of immunomodulatory therapies in treating patients with metastatic melanoma (Hamid *et al.*, 2013; Wolchok *et al.*, 2013). If immune response is important, one would predict that melanomas would behave more aggressively when it is impaired, and there is some evidence for increased melanoma mortality among transplant recipients (Vajdic *et al.*, 2014; Brewer *et al.*, 2011).

Clinical management of transplant recipients would be informed by understanding of risk factors and outcomes for melanoma in this population. Prior studies have been small, and transplant-related risk factors are poorly documented. In the present study, we evaluated the

epidemiology of melanoma in a large population of U.S. transplant recipients and assessed the impact of transplantation on melanoma survival.

Results

Incidence Analysis

A total of 139,991 transplants in non-Hispanic white patients contributed 701,358 person-years of follow-up for incident melanoma (Table 1). Median follow-up time among all transplants was 4.0 years (interquartile range 1.4–7.6 years); this was similar across organ types with the exception of lung recipients who had a median follow-up of 2.6 years. Most transplants occurred in patients who were male (62.9%), aged 35–64 years (69.2%), and received a kidney (50.5%). Transplants of the liver (24.6%), heart (11.7%), lung (5.9%), and other or multiple organs (7.3%) were less common.

Invasive melanoma was diagnosed in 519 transplants and *in situ* melanoma in 190 transplants (incidence rates 74.0 and 27.1 per 100,000 person-years, respectively). Risk of invasive melanoma was elevated more than two-fold above the general population (SIR 2.20, 95%CI 2.01–2.39; Table 2). Although risk was elevated across tumor stages, the greatest increase was for regional stage melanoma (SIR=4.11, 95%CI 3.27–5.09). By tumor site, risk was strongly elevated for melanomas on the head and neck (SIR=3.34, 95%CI 2.85–3.90), with more modest increases for other sites. Risk was also elevated for *in situ* melanoma (SIR=1.47, 95%CI 1.27–1.69, Table 2).

Examination of melanoma risk by stage and time since transplantation revealed two distinct patterns. Risk of regional and distant stage melanoma increased markedly within four years after transplantation (up to 6-fold for regional stage tumors) and then declined, while risk of *in situ* and localized melanoma was elevated approximately 1.5- to 2-fold consistently over time (Figure 1).

To investigate these patterns, we separately evaluated risk factors for localized and regional/distant stage melanoma. Supplemental Table 1 shows adjusted associations for UVR, medications, and transplant-related characteristics, separately according to stage. We did not observe any statistically significant associations with our ecological measures of UVR exposure, thus preventing their inclusion in the final models. However, we note that the trends for localized stage tumors were suggestive (p-values for trend across quintiles of 0.052 for AVGLO and 0.079 for latitude, Supplementary Table 1). In our final multivariable model for localized melanoma (Table 3), higher risk was associated with male sex, increasing age, and azathioprine maintenance therapy (IRR=1.35, 95%CI 1.03–1.77). Compared to kidney recipients, risk was lower in liver recipients (IRR=0.60, 95%CI 0.45–0.80) and lung recipients (IRR=0.50, 95%CI 0.26–0.95). Incidence did not vary significantly by time since transplantation, though it was suggestively higher in some later intervals.

In the multivariable model for regional/distant stage melanoma (Table 3), risk increased with male sex, increasing age, and polyclonal antibody induction therapy (IRR=1.65, 95%CI 1.02–2.67). Incidence increased sharply in the first four years after transplantation before steadily declining.

Survival Analysis

For survival, we evaluated 131,540 patients diagnosed with invasive melanoma, of whom 96% were of white race. Melanomas were largely local stage (76%), with smaller proportions of regional (8%), distant (4%), or unknown stage (13%). Based on linkage to the SRTR, 182 melanomas (0.14%) occurred in transplant recipients.

Over follow-up, 50 transplant recipients (27%) and 16,380 non-recipients (12%) died due to melanoma. Additional deaths were due to other causes (N=42 recipients, N=19,527 non-recipients).

Melanoma-specific mortality was elevated three-fold in transplant recipients compared to non-recipients (HR 2.98, 95%CI 2.26–3.93, Table 4, Figure 2A). This elevation in risk did not vary over time since melanoma diagnosis (likelihood ratio p=0.88) and did not change after restricting to non-Hispanic whites (HR=3.02, 95%CI 2.28–4.01).

After stratifying by melanoma stage, the association of prior transplantation with melanoma-specific mortality was strongest for localized stage melanomas (HR=4.29, 95%CI 2.70–6.82), intermediate for regional stage (HR=3.83, 95%CI 2.34–6.28), and not elevated for distant stage (HR=1.30, 95%CI 0.54–3.13) (Figure 2B–2D). Among localized melanomas, where known, surgical treatment was reported for 96% of transplant recipients and 91% of non-recipients. Restriction to localized melanoma cases with reported surgery did not alter the association with melanoma-specific mortality (HR=4.55, 95%CI 2.82–7.33). Among localized melanomas, mortality appeared increased among transplant recipients for both thin tumors (<1 mm, HR=4.74, 95%CI 2.12–10.6) and thick tumors (≥1 mm, HR=2.14, 95%CI 0.89–5.15).

Discussion

In this large, representative series of solid organ transplant recipients, invasive melanoma incidence was increased over two-fold above rates seen in the general population. We observed notable differences by tumor stage in the timing of onset and melanoma risk factors. Also, melanoma-specific mortality was elevated three-fold compared to non-recipients, suggesting that melanoma behaves aggressively under transplant-related immunosuppression.

One possible interpretation of our results for localized melanoma is that medications that increase UVR-induced DNA damage, coupled with continued UVR exposure, contribute to the development of early melanomas. Incidence of localized tumors was increased in recipients prescribed azathioprine, which may accelerate UVR-induced DNA damage (O'Donovan *et al.*, 2005; Clarke *et al.*, 2015). Additionally, we observed suggestive increases with two measures of UVR exposure, AVGLO (p_{trend} across quintiles = 0.052) and latitude (p_{trend} across quintiles = 0.079) (Supplementary Table 1); we note that these measures are ecological and may not be good proxies for individual-level exposure. Although UVR exposure in early life may be most relevant for melanoma (Nelemans *et al.*, 1993; Holman *et al.*, 1986), the association with azathioprine suggests that UVR exposure occurring after transplantation could also affect risk. One caveat is that we only examined

immunosuppressive medications indicated at baseline. Also, although we adjusted for calendar year of transplantation, there have been strong time trends in medication use, which may have led to residual confounding and impacted these results. Compared to kidney recipients, we observed lower risk for localized melanoma among liver and lung recipients, but we do not have an explanation for this particular result.

For regional and distant stage melanoma, we found a high risk soon after transplantation that may relate to short term, intense immunosuppression. Risk of regional/distant stage tumors peaked within four years of transplantation and increased with T-cell depleting polyclonal antibody induction therapy. Each of these patterns was also observed for melanoma overall in an Australian study (Vajdic *et al.*, 2009). Consistent with a short-term effect of intense immunosuppression, melanoma incidence declines after graft failure in kidney recipients, when patients return to dialysis and immunosuppressive therapy is ceased or reduced (van Leeuwen *et al.*, 2010; Vajdic *et al.*, 2009).

While the steady incidence of localized melanomas after transplantation may represent the occurrence of *de novo* tumors, a plausible explanation for the sharp increase in regional and distant melanoma is that melanocytic precursors or early-stage melanomas were already present but undiagnosed at the time of transplant, and they progressed rapidly with intense immune suppression. Consistent with this model, melanocytic nevus counts increase after transplantation (Grob *et al.*, 1996; Smith *et al.*, 1993), sometimes in an eruptive fashion and/or with presence of dysplasia (McGregor *et al.*, 1991; Barker and MacDonald, 1988). Melanomas express a range of neoantigens that can serve as targets for T-cells (Lennerz *et al.*, 2005), and among melanoma patients, lower host immune response to the tumor (as measured by tumor-infiltrating lymphocytes) is associated with larger tumor size and a greater likelihood of sentinel lymph node positivity (Azimi *et al.*, 2012; Taylor *et al.*, 2007). The excess risk of regional and distant stage melanoma observed here is inconsistent with overdiagnosis, since frequent skin cancer screening in transplant recipients would shift the stage distribution downward (Welch *et al.*, 2005). In passing, we note that melanoma can be transmitted from donors to recipients through the donated organ, but such transmission is very rare and does not likely account for our findings (Strauss and Thomas, 2010; MacKie *et al.*, 2003).

Our survival analysis supports a further role for immune response in controlling melanoma progression after clinical diagnosis. Transplant recipients had a three-fold increased risk of dying from their melanoma compared with melanoma patients without a transplant; this is generally consistent with most (Vajdic *et al.*, 2014; Brewer *et al.*, 2011), but not all (Matin *et al.*, 2008), prior studies. The strong association for localized tumors – including for thin tumors with Breslow thickness <1 mm – implies that there may be subclinical spread of these tumors in transplant recipients, and in turn, that intact immune responses may normally prevent this spread. Importantly, although our data on surgical treatment were limited, our sensitivity analysis did not support that treatment differences explain the decreased survival of transplant recipients. In other contexts, survival following a melanoma diagnosis correlates with multiple measures of the cellular immune response including density, distribution, and activation of tumor infiltrating lymphocytes (Azimi *et al.*, 2012; van Houdt *et al.*, 2008).

Melanoma risk is increased among immunocompromised populations other than transplant recipients (Kubica and Brewer, 2012). HIV-infected people experience an excess (Grulich *et al.*, 2007), but it is smaller, possibly due to differences in the mechanism or rapidity of onset of immunosuppression or to differences in population structure which can confound SIR comparisons. Chronic lymphocytic leukemia (CLL) is a malignancy characterized by immunosuppression, which can be intensified by CLL treatment, and melanoma risk is approximately three-fold increased among CLL patients (Travis *et al.*, 1992; Hisada *et al.*, 2001; Adami *et al.*, 1995). Survival after melanoma may also be decreased in these populations (Brewer *et al.*, 2012; Rodrigues *et al.*, 2002).

Our complementary analyses of melanoma incidence and survival allowed us to assess the impact of immunosuppression along a continuum of outcomes. Linkage of transplant and cancer registries yielded a population-based sample of nearly half of the U.S. transplant population, and cancer registries provided systematic ascertainment of melanomas as well as information on stage, site, and melanoma-specific mortality. Our study is also subject to the typical limitations of analyses based on registry data. We were limited in our ability to assess some clinically relevant information (e.g., tumor Clark's level and Breslow thickness, sentinel lymph node biopsy, details on surgeries) because data were incomplete or unavailable. Our survival analyses were based on death certificate-coded cause of death, which could be inaccurate for transplant recipients who have multiple chronic medical issues. There is also the possibility of differential diagnosis, staging, or reporting of melanoma for transplant recipients compared to non-recipients. For example, transplant recipients may be more likely to be diagnosed with advanced melanomas in hospital settings, where reporting to cancer registries is more complete than for thinner tumors diagnosed in dermatology offices (Cockburn *et al.*, 2008), and because of their poorer health, they may receive a different diagnostic work-up compared to non-recipients. On the other hand, the identification of melanoma may be more difficult among transplant recipients if the frequent presence of other skin lesions makes some melanomas difficult to identify. Finally, while the associations that we observed with melanoma incidence (e.g., for azathioprine maintenance and polyclonal antibody induction) could indicate causal effects, we cannot rule out that they are due to bias, chance, unmeasured confounding factors, or other complexities related to the analysis of linked datasets.

Because risk for multiple types of skin cancer is high, transplant recipients should be encouraged to minimize unnecessary UVR exposure and adopt sun-protective behaviors (Ulrich *et al.*, 2009). Our results also highlight the importance of a thorough dermatologic evaluation for transplant candidates prior to transplantation, with the goal of detecting and removing both small melanomas and precursor lesions that could rapidly progress to invasive melanoma. Close monitoring within 4 years of transplantation is warranted, particularly for recipients with risk factors for late-stage melanoma such as male sex, older age, or receipt of T-cell depleting induction therapy. For transplant recipients who do develop melanoma, physicians should perform an appropriate staging evaluation, including a clinical assessment of lymph node involvement and other distant spread (Fong and Tanabe, 2014). Along with surgery directed at the primary tumor, treatment should

incorporate reduction or revision of immunosuppression, to the extent possible, to facilitate immunologic control of the tumor.

In conclusion, transplant recipients have an elevated risk of melanoma that may be related to immunosuppressive medications used for transplant induction and maintenance. Compared with melanomas in immunocompetent people, melanomas in transplant recipients occur at advanced stage and are associated with poor survival. Evaluation of risk in other immunocompromised populations, as well as molecular characterization of tumors in immunosuppressed patients, may yield further clues to the relationship between immune responses and melanoma.

Methods

Incidence Analysis

The Transplant Cancer Match (TCM) Study (www.transplantmatch.cancer.gov) links the Scientific Registry of Transplant Recipients (SRTR), which captures data on all transplants occurring in the U.S., with 15 population-based cancer registries (Engels *et al.*, 2011). Linkage between the SRTR and cancer registries was performed using a probabilistic matching algorithm based on name, sex, date of birth, and social security number, followed by clerical review of potential matches. The resulting cohort includes 46.5% of the U.S. transplant population during 1987–2010, specifically, transplant recipients in California (years of follow-up: 1988–2008), Colorado (1988–2009), Connecticut (1987–2009), Florida (1987–2009), Georgia (1995–2010), Hawaii (1987–2007), Illinois (1987–2007), Iowa (1987–2009), Michigan (1987–2009), New Jersey (1987–2010), New York (1987–2010), North Carolina (1990–2010), Seattle (1987–2008), Texas (1995–2010), and Utah (1987–2008) (see Table 1 footnote for numbers of transplants by registry). The TCM Study was approved by human subjects research review committees at the National Cancer Institute and, as required, at participating cancer registries.

The outcome for our incidence analysis was first diagnosis of cutaneous melanoma (invasive or *in situ*); subsequent melanoma diagnoses were not further considered. Transplant recipients were followed from the later of transplantation or beginning of cancer registry coverage, and exited at the earliest of melanoma diagnosis, organ failure, a subsequent transplant, loss to follow-up, death, or end of cancer registry coverage. Transplants performed at different times on the same individual were considered separately. We restricted analysis to non-Hispanic whites, as only 26 invasive melanoma cases occurred outside of this group. We further excluded 320 transplants with melanoma diagnosed before transplantation and 128 transplants in people with HIV infection.

We compared melanoma risk in transplant recipients to the general population using standardized incidence ratios (SIRs). SIRs were calculated as the number of observed melanoma cases divided by the number expected, based on general population rates specific to registry, 5-year age group, sex, race/ethnicity, and calendar year. We estimated SIRs overall, by tumor stage and site, and in cross-classified categories by tumor stage and time since transplantation. For tumor stage, we used the summary stage variable, which has three levels (local, regional, and distant) and is largely complete in cancer registries. Summary

stage allows summarization of different and regularly updated clinical staging systems (i.e., American Joint Committee on Cancer editions), thus enabling reliable classification of stage for patients diagnosed over time.

We used zip codes of residence provided by the SRTR to link transplants to two ecological measures of UVR exposure, which we divided into quintiles of equal range (after excluding extreme outliers). The first was latitude, which we assigned using a public database (CivicSpace Labs, 2004). The second was a measure of predicted 30-year average daily global solar radiation (AVGLO) that has been associated with melanoma risk (Tatalovich *et al.*, 2006a; Tatalovich *et al.*, 2006b). Some recipients could not be assigned these measures based on their zip code. For recipients in states where the range of latitude or county-level AVGLO fit completely or very nearly within a pre-defined quintile, we imputed quintiles with a maximum error of 0.5 degrees (latitude) or 41 Wh/km^2 (watt-hours per square kilometer, AVGLO). For latitude, we combined the lower two quintiles (high/highest UVR) due to sparse observation time.

We calculated incidence rate ratios (IRRs) to compare incidence between groups of transplant recipients. We adjusted, *a priori*, for age, sex, transplanted organ, time since transplantation, and year of transplantation (see Table 3 for details). We estimated adjusted IRRs for groups defined by receipt of individual induction and maintenance medications (as recorded at time of transplant), UVR exposure (latitude and AVGLO), and for kidney recipients, living/deceased donor status and history of acute rejection. Based on these results, we included variables with significant IRRs ($p<0.05$) in multivariable Poisson models. As described in the Results, these models were fit separately for localized and regional/distant stage melanoma, because we observed different patterns of incidence over time by tumor stage suggestive of distinct biological processes.

Survival Analysis

To compare survival after melanoma diagnosis between transplant recipients and non-recipients, we used data from a subset of the cancer registries in the TCM Study. Of the 8 registries providing vital status follow-up and cause of death information, we eliminated 2 that appeared to have incomplete follow-up for mortality. Our study population for survival analysis thus included data from Colorado (years of melanoma diagnosis and follow-up: 1988–2009), Connecticut (1987–2009), Georgia (1995–2010), Iowa (1987–2009), New Jersey (1987–2010), and Texas (1995–2010) (see Table 4 footnote for numbers of melanoma cases by registry). Among individuals in the general population who were diagnosed with melanoma (i.e., both transplant recipients and non-recipients), we restricted to melanoma cases occurring as an individual's first diagnosis of invasive cutaneous melanoma (N=134,096). We then excluded cases with missing/unknown cause of death (N=2,556). The survival analysis included patients of all races/ethnicities.

Melanoma patients were classified as transplant recipients if they linked to a transplant in the SRTR that occurred before their melanoma diagnosis. Other individuals were classified as non-recipients. Individuals who received transplants after melanoma diagnosis (N=72) were classified as non-recipients and were censored at transplantation.

The primary survival outcome was death due to melanoma, which we assessed using underlying cause of death codes indicated on death certificates. Follow-up time began at the time of melanoma diagnosis and ended at the first of death, loss to follow-up, or the end of cancer registry ascertainment of deaths. Individuals were censored if they died of another cause or were still living at the end of cancer registry coverage. We calculated melanoma-specific survival estimates using the Kaplan-Meier method.

We fit a Cox proportional hazards model to assess the effect of transplant status, adjusting for age, sex, race, diagnosis year, tumor site, and tumor stage (see Table 4 footnote for details). We tested the proportional hazards assumption for transplant status by allowing different hazard ratios (HRs) for four intervals after melanoma diagnosis (<1, 1–1.9, 2–2.9, and ≥3 years). Separately, we fit models stratified by tumor stage.

We performed three sensitivity analyses. First, we restricted to non-Hispanic whites diagnosed beginning in 1992 (when Hispanic ethnicity data became available). Second, we aimed to assess whether possible treatment differences between transplant recipients and non-recipients influenced survival differences. Localized melanomas comprised the majority of cases, and transplantation was most strongly associated with mortality in this group. Therefore, in the second sensitivity analysis, we restricted to localized cases who were reported by cancer registries to have received surgical treatment. Finally, Breslow thickness was unknown or missing for 42% of melanoma cases, precluding its inclusion in the primary analysis. As a sensitivity analysis, where Breslow thickness was known, we classified localized melanomas as thin (<1 mm) or thick (≥1 mm) and evaluated the effect of transplantation in each category.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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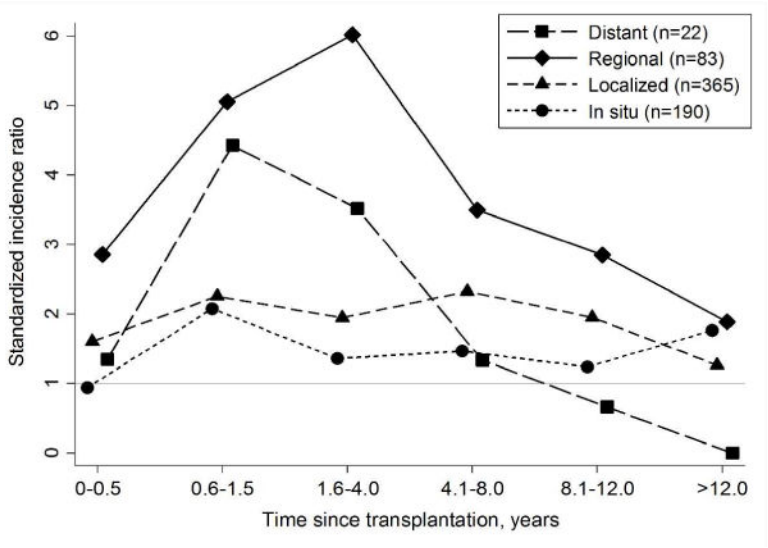

Figure 1.

Standardized incidence ratios comparing melanoma incidence in 139,991 non-Hispanic white transplant recipients to the general population, stratified by time since transplantation and melanoma stage

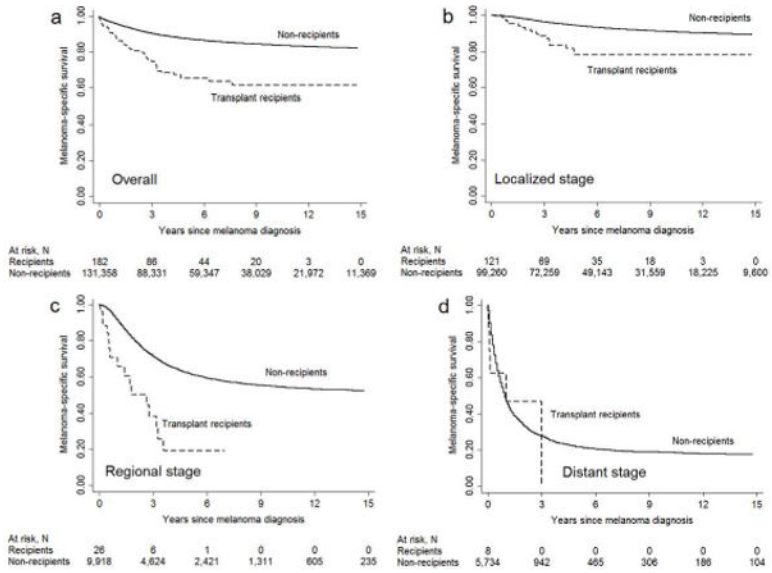

Figure 2.

Melanoma-specific mortality after invasive melanoma for transplant recipients compared to non-recipients, overall and by stage of melanoma

Table 1

Demographic characteristics of 139,991 non-Hispanic white organ transplant recipients, U.S. Transplant Cancer Match Study

Characteristic	N	Percentage
Sex		
Male	88,051	62.9
Female	51,940	37.1
Age at transplantation, years		
0–19	10,619	7.6
20–34	18,519	13.2
35–49	42,267	30.2
50–64	54,598	39.0
65+	13,988	10.0
Transplanted organ		
Kidney	70,729	50.5
Liver	34,487	24.6
Heart	16,325	11.7
Lung	8,243	5.9
Other or multiple	10,207	7.3
Year of transplantation		
1987–1998	53,105	37.9
1999–2002	30,009	21.4
2003–2005	24,185	17.3
2006–2010	32,692	23.4

The cohort includes transplant recipients in California (years of follow-up: 1988–2008, N=22,792 transplants), Colorado (1988–2009, N=4,233), Connecticut (1987–2009, N=3,254), Florida (1987–2009, N=15,703), Georgia (1995–2010, N=6,372), Hawaii (1987–2007, N=298), Illinois (1987–2007, N=12,146), Iowa (1987–2009, N=4,542), Michigan (1987–2009, N=11,720), New Jersey (1987–2010, N=9,550), New York (1987–2010, N=18,500), North Carolina (1990–2010, N=7,859), Seattle (1987–2008, N=4,209), Texas (1995–2010, N=15,915), and Utah (1987–2008, N=2,898).

Table 2

Melanoma risk among 139,991 non-Hispanic white transplant recipients compared to the general population

Melanoma characteristic	Melanoma cases, N	SIR (95% CI)
All invasive melanomas	519	2.20 (2.01, 2.39)
By tumor stage		
Localized	365	2.03 (1.83, 2.25)
Regional	83	4.11 (3.27, 5.09)
Distant	22	2.16 (1.36, 3.27)
Unknown	49	1.88 (1.39, 2.49)
By tumor site		
Head and neck	161	3.34 (2.85, 3.90)
Trunk	162	1.92 (1.63, 2.24)
Lower limbs	117	2.05 (1.70, 2.46)
Upper limbs	49	1.44 (1.07, 1.90)
Other/NOS	30	2.37 (1.60, 3.39)
In situ melanomas	190	1.47 (1.27, 1.69)

NOS, not otherwise specified; SIR, standardized incidence ratio

Table 3

Multivariable models for melanoma incidence among 139,991 non-Hispanic white transplant recipients, stratified by melanoma stage

Characteristic	N*	Localized stage IRR (95% CI)	p_{het}	N*	Regional and distant stage IRR (95% CI)	p_{het}
Attained age, per category†	365	1.85 (1.64, 2.10)		105	1.78 (1.42, 2.24)	
Sex						
Female	92	Reference		23	Reference	
Male	273	1.64 (1.29, 2.09)		82	1.89 (1.18, 3.02)	
Transplanted organ			0.002			0.075
Kidney	203	Reference		54	Reference	
Liver	63	0.60 (0.45, 0.80)		24	0.97 (0.59, 1.60)	
Heart	72	0.91 (0.69, 1.21)		24	1.35 (0.82, 2.22)	
Lung	10	0.50 (0.26, 0.95)		1	0.22 (0.03, 1.61)	
Other or multiple	17	0.89 (0.54, 1.46)		2	0.37 (0.09, 1.52)	
Time since transplantation, years			0.120			0.066
0 – 0.5	21	Reference		5	Reference	
0.6 – 1.5	54	1.42 (0.86, 2.35)		19	2.13 (0.79, 5.71)	
1.6 – 4.0	98	1.26 (0.79, 2.03)		43	2.45 (0.97, 6.23)	
4.1 – 8.0	124	1.63 (1.01, 2.63)		25	1.44 (0.54, 3.86)	
8.1 – 12.0	52	1.46 (0.86, 2.49)		10	1.23 (0.41, 3.75)	
>12.0	16	0.96 (0.49, 1.89)		3	0.86 (0.20, 3.77)	
Year of transplantation			0.306			0.299
1987–1998	189	Reference		46	Reference	
1999–2002	83	1.02 (0.76, 1.38)		31	1.27 (0.79, 2.03)	
2003–2005	60	1.33 (0.95, 1.88)		13	0.79 (0.41, 1.50)	
2006–2010	33	1.29 (0.84, 1.99)		15	1.46 (0.77, 2.78)	
Azathioprine maintenance therapy						
No	235	Reference				
Yes	130	1.35 (1.03, 1.77)				
Polyclonal antibody induction therapy						
No				81	Reference	
Yes				24	1.65 (1.02, 2.67)	

IRR, incidence rate ratio (mutually adjusted), p_{het}, p-value for heterogeneity (likelihood ratio test, provided for variables with more than two levels).

*Number of melanoma cases of the specified tumor stage that occurred in this category.

†Attained age (i.e., current age) was modeled in five categories (0–19, 20–34, 35–49, 50–64, and ≥65 years) with one degree of freedom

Table 4

Comparison of melanoma-specific survival after melanoma diagnosis among 131,540 U.S. transplant recipients and non-recipients

Melanoma characteristic	Melanoma cases, N		Melanoma deaths, N (% of cases)		Adjusted HR for melanoma-specific recipients mortality (95% CI)
	Transplant recipients	Non-recipients	Transplant recipients	Non-recipients	
All invasive melanomas	182	131,358	50 (27%)	16,380 (12%)	2.98 (2.26, 3.93)
By tumor stage					
Localized	121	99,260	18 (15%)	6,229 (6%)	4.29 (2.70, 6.82)
Regional	26	9,918	16 (62%)	3,106 (31%)	3.83 (2.34, 6.28)
Distant	8	5,734	5 (63%)	3,731 (65%)	1.30 (0.54, 3.13)
Unknown	27	16,446	11 (41%)	3,314 (20%)	1.87 (1.03, 3.38)
By thickness, among localized melanomas					
Thin (<1 mm)	59	52,368	6 (10%)	1,674 (3%)	4.74 (2.12, 10.6)
Thick (≥1 mm)	28	16,333	5 (18%)	2,205 (14%)	2.14 (0.89, 5.15)

HR, hazard ratio

The cohort includes melanoma cases in transplant recipients and non-recipients followed for death due to melanoma in Colorado (years of melanoma diagnosis and follow-up: 1988–2009; number melanoma cases = 14,367), Connecticut (1987–2009, N=15,103), Georgia (1995–2010, N=22,331), Iowa (1987–2009, N=11,189), New Jersey (1987–2010, N=31,883), and Texas (1995–2010, N=36,667). Hazard ratios are adjusted for age (in categories of 0–20, 21–30, 31–40, 41–50, 51–60, 61–70, 71–80, 81–90, and >90 years), sex, race (white, non-white), year of melanoma diagnosis (1987–1994–1995–1999–2000–2005, and 2006–2010), and primary site (head and neck, lower limb and hip, trunk, upper limb and shoulder, and overlapping/NOS). The overall hazard ratio for all invasive melanomas is additionally adjusted for tumor stage (localized, regional, distant, unknown).